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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/469,172 06/06/95 SEIDMAN

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EXAMINER

HM12/0414

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MYERS, C
ART UNIT

PAPER NUMBER

1634
DATE MAILED:

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.
08/469,172

Applicant(s)
Seidman et al

Examiner
Carla Myers

Group Art Unit
1634



☒ Responsive to communication(s) filed on Jan 29, 1999

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-30 and 32-47⁴⁶ is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-30 and 32-47⁴⁶ is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

Serial Number: 08/469,172

-2-

Art Unit: 1634

1. This action is in response to Paper No.18, filed January 29, 1999. Applicants arguments presented in the response of Paper No. 18 are essentially the same as those presented in the previous response of Paper No. 14. All arguments have been fully considered but are not persuasive to overcome the grounds of rejection. This action is made FINAL.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
3. Claims 1-30 and 32-⁴⁶47 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 5,429,923. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '923 are inclusive of methods for diagnosing hypertrophic cardiomyopathy wherein the method comprises detecting the presence or absence of a hypertrophic cardiomyopathy associated mutation in the RNA of an individual. It is noted that the claims of '923 do not recite packaging the reagent required to perform the diagnostic method in a kit. However, reagent kits for performing DNA diagnostic assays were conventional in the field of molecular biology at the time the invention was made and therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to package the primers and probes required for the detection of hypertrophic cardiomyopathy associated-mutations in a kit for the expected benefits of convenience and cost-effectiveness.

In the response of Paper No. 18, Applicants state that a terminal disclaimer will be filed upon indication of allowable subject matter if appropriate. Accordingly, the rejection is maintained for the reasons of record.

Serial Number: 08/469,172

-3-

Art Unit: 1634

4. Claim 36 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Eisenberg.

Eisenberg teaches RNA probes complementary to the sequences of the *B*-MHC nucleic acids (see page 289). The probes are considered to have the property of being useful for facilitating diagnosis of hypertrophic cardiomyopathy because the probes of Eisenberg hybridize to and thereby are capable of detecting changes in the *B*-cardiac myosin heavy chain DNA. Accordingly, Eisenberg anticipates the invention of claim 36.

In the response of Paper No. 14, Applicants traversed this rejection by stating that Eisenberg teaches away from the claimed invention because Eisenberg teaches a probe that is not capable of distinguishing between alpha and beta myosin. does not teach or suggest a probe useful for facilitating diagnosis of hypertrophic cardiomyopathy. These arguments are not persuasive because the RNA probe of Eisenberg has the general property of being useful for diagnosing hypertrophic cardiomyopathy because the probe is capable of hybridizing to and detecting *B*-cardiac myosin heavy chain DNA. The claim does not recite any functional or structural language which distinguishes the claimed probe over those of Eisenberg. Any probe which hybridizes to beta-myosin heavy chain DNA would be useful in detecting a mutation in beta-cardiac myosin heavy chain DNA. The claim does not require that the probe facilitate detection by any particular means and does not require that the probe distinguish between beta and alpha myosin. The RNA probe of Eisenberg would be expected to hybridize to the beta-cardiac myosin heavy chain DNA since it is complementary to this DNAs sequence and thereby the probe could be used in, e.g. an enzyme digestion method to detect mutations in the DNA sequence. Again, there is no

Serial Number: 08/469,172

-4-

Art Unit: 1634

requirement in the claim that the probe has the property of specifically hybridizing to only beta-myosin and not hybridizing to alpha-myosin.

5. Claims 37 and 38 are rejected under 35 U.S.C. § 102(a) as being anticipated by Friedman.

Friedman teaches sets of nested PCR primers useful for the amplification of nucleic acids of *B*-MHC (see page 109). Accordingly, Friedman anticipates the invention of claims 37 and 38.

In the response of Paper No. 18, Applicants traverse this rejection by stating that Friedman does not teach primers useful for the detection of hypertrophic cardiomyopathy and assert that Friedman teaches away from the claimed invention because the reference teaches that mutations could not be identified in exon 13 of patients with MHC. These arguments are not persuasive because it is a property of the primers taught by Friedman that they are useful in the diagnosis of hypertrophic cardiomyopathy because the primers are capable of amplifying the *B*-MHC DNA and thereby could be used for diagnostic analysis of the sequences of the amplified *B*-MHC DNA. Applicants appear to be asserting that Friedman must teach use of the probe for detecting hypertrophic cardiomyopathy mutations. However, the claims are not drawn to methods for detection of hypertrophic cardiomyopathy mutations, but rather are drawn to a set of primers. Again, it is a characteristic of the primers of Friedman that they are useful for detecting hypertrophic cardiomyopathy mutations. There is no requirement that Friedman teach all properties of a product. The issue is whether the product taught in the art is the same as the product claimed. In the instant case, the primers of Friedman are indistinguishable from the primers claimed.

6. Claims 37 and 38 are rejected under 35 U.S.C. § 102(b) as being anticipated by Feldman.

Serial Number: 08/469,172

-5-

Art Unit: 1634

Feldman teaches compositions comprising sets of PCR primers useful for the amplification of nucleic acids of *B*-MHC (see page 1867). The compositions of Feldman contain 13 pmol of each primer and therefore are considered to comprise at least 4 oligonucleotides. Accordingly, Feldman anticipates the invention of claims 37 and 38.

In the response of Paper No. 14, Applicants traverse this rejection by stating that Feldman teaches gene expression of *B*-MHC by PCR, but does not teach primers useful for facilitating the diagnosis of hypertrophic cardiomyopathy. It is stated that amplification alone does not provide the utility of detecting a mutation. However, the ability of the set of primers to amplify a sequence which contains a mutation means that the primers have the property of being useful for detecting a mutation since the sequence amplified can then be analyzed, e.g. by sequencing, for the presence of a mutation. Applicant appears to be reading limitations into the claims. The claims do not require that the primers hybridize to a specific mutation, as with allele specific primers which amplify only a mutated form of the sequence and not wild-type sequence, or vice-versa. Rather, the instant claims require only that the primers be useful, in any way, for detecting a mutation in *B*-MHC. Again, it is a characteristic of the primers taught by Feldman that they are useful in the diagnosis of hypertrophic cardiomyopathy because the primers are capable of amplifying the *B*-MHC DNA and thereby could be used for diagnostic analysis of the sequences of the amplified *B*-MHC DNA. Applicants claimed primers are not distinguishable by functional or structural limitations over the primers of Feldman.

7. Claims 33-35 are rejected under 35 U.S.C. § 103 as being unpatentable over Geisterfer-Lowrance in view of Almoguera and further in view of the Stratagene Catalog.

Serial Number: 08/469,172

-6-

Art Unit: 1634

Geisterfer-Lowrance teaches methods for detecting the presence of mutations associated with hypertrophic cardiomyopathy wherein the methods comprise detecting the presence of point mutations in the *B*-MHC nucleic acids by isolating DNA from individuals affected with hypertrophic cardiomyopathy and sequencing the DNA in order to identify the presence of mutations associated with hypertrophic cardiomyopathy (see, e.g., page 1000). In particular, Geisterfer discloses the presence of the missense mutation Arg403Gln and the association of this mutation with individuals having hypertrophic cardiomyopathy. Geisterfer-Lowrance does not teach detecting point mutations associated with hypertrophic cardiomyopathy by first amplifying sample *B*-MHC nucleic acids and performing a RNase protection assay.

Almoguera teaches methods for identifying gene mutations associated with genetically inherited diseases wherein the methods comprise amplifying a DNA sequence by PCR, combining the amplified DNA with a labeled RNA probe in order to form a RNA/DNA hybrid, and performing an RNase protection assay wherein cleavage of the RNA/DNA at regions that are not hybridized as indicative of the presence of a disease associated mutation (see, for example, pages 39-41). In particular, the assay identifies single-base substitutions or point mutations which are considered to be "small alterations" in the DNA. Almoguera states that this provides a very rapid, efficient and sensitive means for detecting the presence of point mutations associated with diseases.

In view of the disclosure of Almoguera, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Geisterfer-Lowrance so as to have detected the mutations associated with hypertrophic myocardiopathy in

Serial Number: 08/469,172

-7-

Art Unit: 1634

B-MHC nucleic acids by amplifying the nucleic acids by PCR and detecting the presence of mutations by performing an RNase protection assay using a labeled RNA probe in order to have achieved the expected advantages of providing a more rapid, efficient, and sensitive assay for the detection of hypertrophic cardiomyopathy associated mutations in *B*-MHC nucleic acids.

Modification of the method of Geisterfer-Lowrance as discussed above would have resulted in a method for detecting point mutations in the *B*-MHC gene which required the use of the reagents of an RNA probe hybridizable to the *B*-MHC gene, PCR primers for the amplification of the *B*-MHC gene and a RNaseA for digesting unhybridized RNA. It is noted that at the time the invention was made the complete nucleotide sequence of the *B*-MHC was well known in the art and therefore the generation of primers and probes to perform the amplification/RNase protection assay of Almoguera would have been obvious to one of ordinary skill in the art and well within the skill of the ordinary artisan. The combined references do not teach packaging these reagents required to practice the detection method or instructions for the detection method in a kit.

However, reagent kits for performing nucleic acid diagnostic assays were conventional in the field of molecular biology at the time the invention was made. In particular, the Stratagene catalog discloses the general concept of kits for performing nucleic acid detection methods and discloses that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primers, RNA probe, and RNase in a kit for the

Serial Number: 08/469,172

-8-

Art Unit: 1634

expected benefits of convenience and cost-effectiveness for practioners of the art. With respect to claim 35, it would have been further prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included instructions in the kit in view of the conventionality of including instructions in kits for facilitating the use of the packaged reagents. It is noted that the written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight (see MPEP 706.03(a)).

In the response of Paper No. 18, Applicants traverse this rejection by stating that Geisterfer-Lowrance only demonstrates that afflicted members of a single family with FHC have the mutation and that in the absence of extensive studies on the correlation between the mutation and MHC. It is stated that at the time the invention was made it was possible that HC could be due to a point mutation at amino acid 403 of *B*-MHC, an alpha/beta cardiac myosin heavy chain hybrid gene or a mutation that had not yet been described in the art. Applicants point out that the instant invention provides evidence that mutations can be used as an indicator of HCM. It is argued that there would not have been a reasonable expectation of success of the claimed methods or a suggestion for a collection of reagents in a kit. It is further stated that Geisterfer-Lowrance teaches away from the claimed invention because this reference states that since the mutation has been characterized in only two families, it cannot be predicted whether most individuals bear either of the two identified alleles, or whether the disease results from other new mutations.

Applicants arguments have been fully considered but are not persuasive. It is pointed out that the instant claims are drawn to products, not methods, and in claims to products, such as kits,

Serial Number: 08/469,172

-9-

Art Unit: 1634

the intended use of the product carries no weight. While the teachings of Geisterfer-Lowrance may not have been sufficient to enable absolute diagnosis of HCM, the prior art suggests use of the disclosed sequences to amplify *B*-MHC nucleic acids and to identify mutations. Applicants arguments suggesting that the prior art must teach an unequivocal ability to diagnose HCM using primers is not appropriate for the instant rejection over claims to KITS. The intended use of the reagents in the kit does not carry any weight with respect to the obviousness of the invention. Thus, the prior art when considered as a whole would have suggested the claimed kits for the benefits of convenience and cost-effectiveness for practioners of the art wishing to amplify and identify mutations in the *B*-MHC nucleic acids. Again, it is pointed out that there is no requirement for the art to teach that the mutations identified by Geisterfer-Lowrance could be used to diagnose HCM. The art when considered as a whole provides sufficient motivation to generate a kit containing the components of primers for *B*-MHC for the detection of mutations in the MHC gene. Applicants state that instructions provide a guide to the user of choice of one or more probes or primers and teaches conditions for performing PCR. Therefore, Applicants conclude that the printed subject matter in instructions makes the kits distinct over those suggested in the prior art. Firstly, Applicants kits recite only "instructions for using the components of the kit to detect the presence or absence of a hypertrophic cardiomyopathy-associated mutation". Applicants claims do not require that the instructions include any particular subject matter concerning how to use the primers and probes and what conditions of amplification or hybridization would be required with each primer or probe. Accordingly, the instructions that would be provided to perform the method of Geisterfer-Lowrance would not be distinct over

Serial Number: 08/469,172

-10-

Art Unit: 1634

those of Applicant. In any event, the printed subject matter is immaterial since printed subject matter is not patentable and thereby the "typed words" of an instruction manual do not carry any weight. As discussed in MPEP 706.03(a), "a mere arrangement of printer matter" is not within the statutory classes" and therefore the printed material does not carry weight in the claim.

Accordingly, Applicants comments regarding the fact that printed instructions would provide information as to how to analyze positive and negative results is not persuasive because Applicant is arguing limitations that are not present in the claims.

8. Claims 24-26, 28-30 and 43 are rejected under 35 U.S.C. § 103 as being unpatentable over Geisterfer-Lowrance in view of Mullis.

Geisterfer-Lowrance teaches methods for detecting the presence of mutations associated with hypertrophic cardiomyopathy wherein the methods comprise detecting the presence of point mutations in the *B*-MHC nucleic acids by isolating DNA from individuals affected with hypertrophic cardiomyopathy and sequencing the DNA in order to identify the presence of mutations associated with hypertrophic cardiomyopathy (see, e.g., page 1000). In particular, Geisterfer discloses the presence of the missense mutation Arg403Gln and the association of this mutation with individuals having hypertrophic cardiomyopathy. The reference (see abstract) states that the "(I)dentification of two unique mutations within cardiac MHC genes in all individuals with FHC from two unrelated families demonstrates that defects in the cardiac MHC genes can cause this disease". Geisterfer-Lowrance does not teach amplifying the sample *B*-MHC nucleic acid prior to determining the sequence of the DNA.

Serial Number: 08/469,172

-11-

Art Unit: 1634

Mullis teaches methods for amplifying nucleic acids by the method of PCR and applies this methodology to assays to detect the presence of point mutations in nucleic acids associated with genetic diseases (see, e.g. col. 2, and 18). Mullis also teaches amplifying nucleic acids by PCR prior to sequencing (see column 36). The reference states that PCR provides the advantages of increasing the quantity of the target nucleic acid and thereby increases the sensitivity of nucleic acid detection and characterization assays. Mullis further teaches that the presence of mutations associated with a disease can be detected in a sample RNA by first reverse transcribing the RNA to DNA, amplifying the DNA by PCR and then analyzing the amplified DNA for the presence of disease associated mutations.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Geisterfer-Lowrance so as to have amplified the B-MHC nucleic acids prior to sequence analysis in order to have increased the quantity of the target DNA and thereby to have increased the overall sensitivity of the detection of hypertrophic cardiomyopathy associated point mutations in the *B*-MHC nucleic acids.

In the response of Paper No. 18, Applicants argue that there is no expectation of success for formulating the claimed methods and state that there is no suggestion in the cited references for formulating a method a method or kit for detecting mutations associated with HC. These arguments are not persuasive because the claims are not directed to methods of diagnosis but rather only to methods for identifying mutations in the *B*-MHC gene. Applicants arguments that the prior art must teach that a specific mutation is unequivocally associated with HC is inappropriate because the claims do not require diagnosis of HC. The claims are drawn only to

Serial Number: 08/469,172

-12-

Art Unit: 1634

methods to detect a mutation associated with HC. Geisterfer-Lowrance provides the motivation and reasonable expectation for identifying such mutations in other nucleic acid samples because the reference provides the methodology for detecting such mutations and it would have been well within the skill of the art to have practiced these conventional methods to effectively accomplish the analysis of nucleic acids for mutations. Furthermore, the reference provides the motivation to analyze additional samples for the stated mutations because the reference teaches that further assays should be performed to determine if the mutation is present in other families and states that use of genetic probes to MHC mutations will be important in facilitating our understanding of the function of MHC and the causes of HC. Accordingly, the cited prior art suggests and provides a high expectation of success of employing methods for the detection of mutations in MHC. It is stated that neither Geisterfer-Lowrance nor Mullis teach "how to diagnose a subject who might carry a mutation within a 30,000 bp gene". These arguments are not persuasive because the claims do not require detecting every mutation possible over a 30 kbp gene, but simply require detecting a mutation. Secondly, the claims are not drawn to methods for diagnosing HCM, but are rather are drawn to methods for identifying a mutation associated with HCM. Since the combined prior art teaches a method for effectively detecting a mutation, which mutation has the property of being associated with HCM, the prior art when considered as a whole leads the ordinary artisan to a method for detection of a HCM associated mutation. Again, there is no requirement for the claims as written that the prior art further teach that one can then use this information to diagnose a patients susceptibility to HCM.

Art Unit: 1634

9. Claim 27 is rejected under 35 U.S.C. § 103 as being unpatentable over Geisterfer-Lowrance in view of Almoguera.

Geisterfer-Lowrance teaches methods for detecting the presence of mutations associated with hypertrophic cardiomyopathy wherein the methods comprise detecting the presence of point mutations in the *B*-MHC nucleic acids by isolating DNA from individuals affected with hypertrophic cardiomyopathy and sequencing the DNA in order to identify the presence of mutations associated with hypertrophic cardiomyopathy (see, e.g., page 1000). In particular, Geisterfer discloses the presence of the missense mutation Arg403Gln and the association of this mutation with individuals having hypertrophic cardiomyopathy. Geisterfer-Lowrance does not teach detecting point mutations associated with hypertrophic cardiomyopathy by first amplifying sample *B*-MHC nucleic acids and performing a RNase protection assay.

Almoguera teaches methods for identifying gene mutations associated with genetically inherited diseases wherein the methods comprise amplifying a DNA sequence by PCR, combining the amplified DNA with a labeled RNA probe in order to form a RNA/DNA hybrid, and performing an RNase protection assay wherein cleavage of the RNA/DNA at regions that are not hybridized as indicative of the presence of a disease associated mutation (see, for example, pages 39-41). In particular, the assay identifies single-base substitutions or point mutations which are considered to be "small alterations" in the DNA. Almoguera states that this provides a very rapid, efficient and sensitive means for detecting the presence of point mutations associated with diseases.

Serial Number: 08/469,172

-14-

Art Unit: 1634

In view of the disclosure of Almoguera, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Geisterfer-Lowrance so as to have detected the mutations associated with hypertrophic cardiomyopathy in *B-MHC* nucleic acids by amplifying the nucleic acids by PCR and detecting the presence of mutations by performing an RNase protection assay using a labeled RNA probe in order to have achieved the expected advantages of providing a more rapid, efficient, and sensitive assay for the detection of hypertrophic cardiomyopathy associated mutations in *B-MHC* nucleic acids.

In the response of Paper No. 18, Applicants traversed this rejection for the reasons stated above. Accordingly, the response to those arguments apply equally to the present grounds of rejection.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Serial Number: 08/469,172

-15-

Art Unit: 1634

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-305-3014 or (703)-305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers
April 14, 1999

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER